REMARKS

Claims 1-7 are canceled. Claims 9-11 were amended. New claims 12 to 15 were added. New claims 12-15 are supported by claims 10-11 as well as the examples. New claims 14 and 15 are also supported by the "Description of the Symbols in the Drawings" and Figure 1.

Newly Applied Rejections/Objections

Claim Objections

Claims 9, and 10-11 were objected to because of various informalities. The claims were corrected as suggested by the Examiner. Claim 9 was amended to recite, "wherein the acrylic component of the acrylic pressure sensitive adhesive is selected from at least one of the following …". Claims 10 and 11 were amended to remove the word "further."

Claim Rejections – 35 USC § 103

In new claims 12 and 13, the laminate structure of the backing of the external patch is low-density polyethylene film having a thickness of 1 to 200 μm as the outermost layer and polyethylene terephthalate film (PET) having a thickness of 0.1 to 10 μm as the next and the drug non-adsorptive layer. Applicants maintain that in a case where the low-density polyethylene film was used as backing layer for the external patch by itself, a large amount of free volume (i.e., void structure) of said film is necessary to secure the flexibility of the backing. Accordingly, when the adhesive layer containing active ingredient applies onto said backing with just low-density polyethylene film, the adsorption of the active ingredient from the adhesive layer into the backing layer occurs in association with free volume of the film, and this phenomenon constitutes a limiting factor of percutaneous absorption of the active ingredient. (See page 5, lines 12-22 of the specification as filed ("Background Art") for discussion). However, in the case of present disclosure and claims, the high-density[1] polyethylene terephthalate film having a

[1] See page 18, line 8 of the specification as originally filed and surrounding discussion.

thickness of 0.1 to 10 μm acts as a drug non-adsorptive layer, to prevent the adsorption of the active ingredient from the adhesive layer into the backing layer.

Claims 9-10 were rejected under 35 U.S.C. 103(a) as being unpatentable over Kawaji et al. (US 6,177,098) in view of Akemi et al. (US 5,242,951).

The **orientation of the layers** in the patches of Kawaji and the present application are **opposite.** Kawaji et al. describes the polyester film, which can be "composed mainly by polyethylene terephthalate"[2] to be used as the outermost layer, see for example, column 4, lines 15-27, which states:

> "The polyester film, in general, has the glassy finished surface and reflects the outside light when applied to the skin. This lustrous cause the plaster to be seen low in quality. Therefore, to gain high quality look for the plaster, the surface of the polyester film preferably be processed with emboss treatment. ..."

The Kawaji reference teaches the polyethylene terephthalate layer to clearly be on the surface, visible when the patch is applied to the skin. Otherwise, its appearance would be unimportant.

The Kawaji reference goes on to describe "spreading the adhesive base material containing the active ingredient onto the non-woven fabric side of the laminated backing." Kawaji teaches a patch as follows:

Outside Air

1. PET layer
2. Non-woven layer
3. Adhesive layer containing active ingredient

Skin

[2] Column 3, lines 52-53 of Kawaji et al. patent.

In contrast, the present application describes the following:

Outside Air

1. Flexible film
2. PET layer
3. Adhesive containing female hormone

Skin

The present application describes the opposite orientation and results in a completely different external patch than the one taught by the Kawaji reference. This distinction is present in the prior claims 10 and 11 wherein it was stated that the pressure-sensitive adhesive is adjacent to the drug non-adsorptive layer. To emphasize this point, the present amendments emphasize the placement of the various layers. The new claims also clearly indicate the orientation of the different layers in the patch. If the examiner feels alternate language is clearer, she is respectfully requested to contact the undersigned.

The specific thickness of the flexible film layer is significant. As stated on page 18, line 28 to page 19, line 6 of the specification as originally filed:

> If the thickness of the flexible film layer is less than 1 μm, it is difficult to apply a preparation to the skin because the preparation is bent or warped when the release liner is removed due to the lack of elasticity. On the other hand, if the thickness of the flexible film layer exceeds 200 μm, it becomes difficult for a preparation to follow the irregularities on the skin surface or body movements so that the transdermal absorbability of an active ingredient is lowered.

Applicants respectfully maintain that it is unobvious to one skilled in the art to modify the teaching of Kawaji to come out up this exact range of the present claims, especially when Kawaji provides no indication of any range or parameters for thickness of the nonwoven layer other than "appropriateness."

The structure of the Akemi et al. enstrogen-containing gel structure is as follows:

Outside Air

1. Nonporous sheet
2. Porous film
3. Crosslinked gel layer on surface of the porous sheet containing estrogen

Skin

The Akemi et al. reference is significantly different from the external patch disclosed and claimed herein. The only way to even locate isocyanate crosslinking in the Akemi et al. reference is to take the present disclosure and use it and hindsight to find the isocyanate crosslinking in Akemi. One skilled in the art would have no motivation or teaching to take isocyanate crosslinking out of the Akemi reference and combine it with the Kawaji et al. reference to obtain the present claims. Akemi et al describes many ways of cross-linking including "physical means such as irradiation (for example, UV irradiation or electron beam irradiation) or a chemical means with the use of a cross-linking agent (for example, polyisocyanate compound, organic peroxide, organic metal salt, metal alcholate, metal chelate compound, polyfunctional compound)." Column 4, line 67 - column 5, line 5, of the Akemi et al., U.S. Patent 5,242,951.

Making a selection from a reference based only on the disclosure of the application under review is the situation where "obvious to try" is erroneously equated with obviousness under §103. In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988). The Court of Appeals for the Federal Circuit goes on to explain that in this class of case,

> what would have been "obvious to try" would have been to vary all the parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

Id. Isolating polyisocyanate out of the Akemi et al patent is really throwing "metaphorical darts at board filled with combinatorial prior art possibilities," a practice

that the Federal Circuit recently warned against, as succumbing "to hindsight claims of obviousness" in In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

Moreover, one would not look to the Akemi et al. reference to obtain the external patch disclosed or claimed in to the present application due to the significant differences, in particular the liquid plasticizer which is so prominently part of the Akemi et al. disclosure. These differences have already been discussed in detail in the Amendment dated May 12, 2008 on pages 5-8 and those arguments are part of the present response. A copy of the May 12, 2008 Amendment is attached as an exhibit to the present response.

Claims 9 was rejected under 35 U.S.C. 103(a) as being unpatentable over Kawaji et al. (US 6,177,098) in view of Akemi et al. (US 5,242,951) and further in view of Radloff et al. (WO 2002/038134). US 2004/0091521 is used as an English equivalent translation of WO 2002/038134.

The Examiner pointed out that Radloff et al. discloses a backing having a laminate structure comprising polyethylene terephthalate and a flexible film made of low-density polyethylene. Furthermore, the Examiner pointed that it would have been obvious to one of ordinary skill in the art to modify the materials of the backing of Akemi et al. to be that of Radloff et al. in order to provide the desired effect and elasticity/flexibility.

Radloff et al. describes an active substance patch comprising a laminate coated on its skin-facing side with an adhesive which comprises an active substance, the laminate having at least two plies. The side of the patch far remote from the skin is a barrier layer, which is impervious to the active substance, while its skin-facing side is a backing layer, and these two layers can be separated from one another.

Radloff teaches a patch as follows:

Outside Air

1. Barrier layer
2. Backing layer
3. Adhesive layer containing active ingredient

Skin

Like Akemi, Radloff is the opposite orientation from the external patch of the present application. Applicants respectfully maintain that the orientation is presently specified and claimed in the pending claims and therefore these claims are patentable over prior art that relies on an alternate orientation.

Claims 9 and 11 are rejected under 35 U.S.C. §103(a) as being unpatentable over Xia et al. (US 5,693,335) in view of Hoffmann et al. (US 5,393,529) and further in view of Muraoka et al. (US 5,876,745)

The Xia et al patent describes its disclosure as follows:

"One aspect of the invention is a matrix for use in administering sex steroids transdermally comprising a mixture of:

a) a pressure-sensitive adhesive;

b) a sex steroid; and

c) a skin permeation enhancer comprising a mixture of:

(i) a polyhydric thioalcohol of 2 to 6 carbon atoms having at least one mercapto group and at least one hydroxy group; and

(ii) an aliphatic carboxylic acid of 8 to 24 carbon atoms or an ester of said acid.

Another aspect of the invention [the Xia reference] is a transdermal patch for administering a sex steroid comprising a laminated composite of:

a) a backing layer; and

b) a layer of the above described matrix underlying the backing layer."

(Column 1, lines 59 to Column 2, line 9 of the Xia reference). Isopropyl myristate is only one of literally hundreds of aliphatic carboxylic acids and esters taught by the Xia reference (See, column 3, lines 19-30). There is nothing in Xia, Hoffman or Muraoka references separately or together that would designate isopropyl myristate specifically and particularly in combination with norethisterone. Xia teaches a polyhydric thioalcohol of 2 to 6 carbon atoms having at least one mercapto group and at least one hydroxy group as a **critical element**. It would not be obvious to a person having ordinary skill in the art to look at Xia and eliminate the polyhydric thioalcohol. There is no conceivable reason or teaching for taking the polyhydric thioalcohol away from the skin permeation enhancer taught by Xia et al.

The Xia et al. composition is another example where the impermeable layer (drug non-adsorptive layer) is the outermost layer, farthest away from the skin. As stated in column 3, lines 39:

"The backing layer of these patches is impermeable to the drug and other components of the patch and defines the top face surface of the patch." (Emphasis added). In contrast, the present application and claims teach the drug-permeable low density polyethylene film as the top face surface of the patch.

The Hoffman et al. patent describes isocyanate based cross-linking agents but also suggests cross-linking agents based on acetonates, titanates, polyfunctional propyleneimine derivatives, etherified melamine formaldehyde resins, highly methylated urethane resins and imino-melamine resins. There is nothing in Hoffman or even Xia and Muraoka that would lead one to preferentially use isocyanates out of the Hoffmann et al. list of cross-linking agents. In addition, the whole focus of the Hoffmann reference is "water-swellable polymers added to the adhesive mass of the active substance containing plaster" (Column 4, lines 32-49). Hoffmann et al. includes a long list of other substances such as tackifying resins, crystallization inhibitors, long-chain alcohols, etc., none of which are called for in the patches taught by the present application.

Finally, the laminate structure of Muraoka et al comprises a non-porous sheet and a porous sheet. The porous sheet is clearly not a drug non-adsorption layer. The non-porous layer is preferred to be impermeable to the drug. However, the Muraoka et al. teaches the nonporous layer to be the outermost layer unlike the present application. Muraoka teaches a patch as follows:

Outside Air

1. Non-porous sheet
2. Porous sheet
3. Adhesive layer containing active ingredient

Skin

(Column 6 of Muraoka et al.) The drug non-adsorptive layer (non-porous layer) and the adsorptive layer (porous) are once again in the opposite orientation from the present application.

Claims 8 was rejected under 35 U.S.C. §103(a) as being unpatentable over Xia et al. in view of Hoffmann et al. and further in view of Muraoka et al. and further in view of Radloff et al.

The above discussions of the Xia, Hoffmann, Muraoka and Radloff references also apply to this rejection.

In summary, applicants provides the following table:

	APPLICATION NO. 10/524,065	KAWAJI	AKEMI	RADLOFF	MURAOKA
	Outside Air	Outside Air	Outside Air	Outside Air	Outside Air
1	Non-woven layer	PET layer (barrier layer)	Non-porous sheet (barrier layer)	Barrier layer	Non-porous sheet (barrier layer)
2	PET layer (barrier layer)	Non-woven layer	Porous sheet	Backing layer	Porous sheet
3	Adhesive containing female hormone	Adhesive layer containing active ingredient	Cross-linked gel layer containing active ingredient	Adhesive layer containing active ingredient	Adhesive layer containing active ingredient
	Skin	Skin	Skin	Skin	Skin

The orientation of the "layers" in applicants' patch has an opposite orientation from the patches described in the references. Applicants respectfully maintain that applicants' patch is not obvious in light of the cited references. There is nothing in any of the references that would in anyway teach or suggest the reversal of the barrier layer from the outside to immediately next to the adhesive or gel layer containing the active ingredient. In addition, there is nothing in the cited references that would lead one to use the particular ingredients used in applicants' patch or delete the additional ingredients described in the references. The claims as amended and the new claims have tried to clearly define the invention, including the use of "consisting" to eliminate the possibility of additional layers being added to the patch or additional ingredients in the adhesive layer.

CONCLUSION

If the Examiner has any questions or suggested Examiner's amendments, the Examiner is respectfully requested to call the undersigned.

The Commissioner is hereby authorized to charge any additional fees, or to credit any overpayment, to Deposit Account No. 50-3195.

Respectfully submitted,

Date: May 7, 2010

/Manette Dennis/

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Appendix
1. May 12, 2008 Response (previously filed)